III. REMARKS

Examiner objects to Figure 1A as unreadable. In response to Examiner's objection, Applicants request that Figure 1A be replaced by Figure 1A enclosed herein. No new matter has been added.

Claims 7, 9-40, 42-48, 50, 60, 61, and 73-75, which are drawn to non-elected inventions, have been canceled, without prejudice to Applicants' right to pursue the subject matter in a related application. Claims 62 and 76 are amended to clarify the claim language and are supported by the specification. Claim 67 is amended to more clearly claim the invention and is supported by the specification. New claims 82-88 have been added. Support for these claims 82-88 is found in the specification at:

Claim	Support in the Specification
82	Specification, pp. 10, l. 15 to p. 12, l. 2 and pp. 42-71
83	Specification, pp. 34-38
84	Specification, p, 17, ll. 16-17.
85	Specification, p. 17, ll. 17-18.
86	Specification, p. 17, ll. 13-15.
87	Specification, p. 24, l. 20 to p. 25, l. 25.
88	Specification, p. 25, ll. 10-25

After entry of this amendment, claims 62-72 and 76-88 will be pending. No new matter has been added.

A. The Claimed Invention

Tat protein is 86-102 amino acids, depending on the viral strain and is coded by two exons, the first exon being conserved among different viral isolates. Specification, p. 2, ll. 14-19, citing Myers *et al.*, Human Retroviruses and AIDS: A compilation and analysis of nucleic acid and amino acid sequences, Los Alamos Laboratory, Los Alamos, NM, p. 1 (1993). Tat protein is produced soon after infection and plays a critical role in viral replication and transmission. Specification, pp. 2-3, citing to Chang *et al.*, AIDS 11: 1421 (1997). Tat protein also modulates the survival and proliferation of infected and non-infected cells by causing activation or repression of cytokines or genes that play a key role in the cell cycle. *Id.*

Anti-Tat cell-mediated responses in the initial phase of HIV infection have been shown to be important in the control of the infection itself. Specification, p. 5, citing Voss *et al.*, Virology 208:770 (1995), Rinaldo *et al.*, AIDS Res. Hum. Retrov. 11:481 (1995), and Harrer *et al.*, AIDS Res. Hum. Retrov. 12:585 (1996). The presence of specific anti-Tat CTLs has been inversely correlated with AIDS progression. Specification, p. 5, citing van Baalen *et al.*, J. Gen. Virol., 77: 1659 (1996).

Prior to the present invention, those of skill in the art believed that administration of tat protein would enhance viral replication in infected subjects and/or induce immunosuppression in seronegative or seropositive individuals, *i.e.*, would have significant adverse effects. See Specification, p. 10, ll. 4-8. However, as Applicants discovered and as shown by the examples in specification, administration of the biologically active tat protein of the present invention actually results in protective immune responses against AIDS and other HIV related diseases and is safe. See Specification, Example 4, particularly p. 71, ll. 9-19 and p. 51, ll. 13-15.

The specification defines the term "biologically active tat protein" as tat protein that, at picomolar or nanomolar concentrations

i) enters and localizes in the nuclei of activated endothelial cells or dendritic cells

ii) activates the proliferation, migration, and invasion of Kaposi's sarcoma ("KS") cells and cytokine-activated endothelial cells protein

iii) activates virus replication when added to infected cells as measured by

   a) the rescue of tat-defective proviruses in HLM-1 cells after the addition of exogenous protein

   b) the transfection of HIV-1 gene expression in cells transfected with a HIV-1 promoter-reporter plasmid protein

and

iv) induces in mice the development of KS-like lesions in the presence of angiogenic factors or inflammatory cytokines.

See Specification, p. 14, l. 28 to p. 15, l. 11. The specification also discloses that biologically active tat protein of the invention is purified in such a way that oxidation and aggregation of tat protein's cysteine residues is prevented. Specification, Example 1. Oxidation and aggregation of a protein's cysteine residues can form intra- and inter-molecular bonds that modify the protein's conformation and, thus, functionality. Specification, p. 24, ll. 22-24.

Therefore, by purifying and isolating tat protein using methods that ensure that the tat protein's cysteine residues do not oxidize or aggregate, biologically active tat protein can be obtained. The specification describes such a method as a non-limiting example in Example 1. If the tat protein is oxidized or aggregated, it is not "biologically active tat protein" as defined by the specification.

Some references in the art disclose so-called "biologically active tat protein" that does not meet the definition of "biologically active tat protein" of the present specification. The biologically active tat protein of the present invention differ from tat protein used previously in the art by functions recited in the claims, including the ability of biologically active tat protein to enter endothelial and dendritic cells at low concentrations. The uptake of biologically active tat protein by endothelial and dendritic cells at low concentrations is mediated by $\alpha_5\beta_1$ and $\alpha_v\beta_3$ receptors through the interaction with the arginine-glycine-aspartic acid sequence ("RGD") of the carboxy-terminal portion of the second exon of the tat protein. Specification, p. 33, ll. 25-30. Although tat protein without the RGD motif, *i.e.*, not biologically active, can be taken up by cells, higher concentrations of the tat protein are required since uptake of the tat protein occurs through an integrin-independent pathway. *Id.* Thus, so-called "biologically active tat protein" disclosed in references in the art in which tat protein is taken up by cells at high concentrations, *e.g.*, greater than 10 nM, is not biologically active tat protein of the present invention.

Claim 62, upon which claims 63-66 depend, is directed to a pharmaceutical composition comprising biologically active isolated tat protein, fragments thereof, and/or mutants in combination with suitable recipients and/or diluents. Claim 63 is directed to the pharmaceutical composition wherein the biologically active tat protein of the pharmaceutical composition of claim 62 is lyophilized for storage and resuspended for use. Claim 64 is directed to the use of the pharmaceutical composition as a vaccine for use in the treatment of AIDS and conditions associated with HIV infection. Claim 65 is directed to the pharmaceutical composition of claim 62 comprising biologically active tat protein that is identified as SEQ. ID. NO 2.

Claim 67, upon which claims 68-72 depend, is directed to a pharmaceutical composition comprising biologically active isolated tat protein wherein the tat protein is obtained by a purification process that prevents its oxidation and aggregation. Claim 68 is directed to the pharmaceutical composition of claim 67 wherein the tat protein is purified using heparin affinity chromatography. Claim 69 is directed to the pharmaceutical composition of claim 68 wherein the purified tat protein is stored in lyophilized form and

then resuspended in a degassed buffer. Claim 70 is directed to the use of the pharmaceutical composition according to claim 67 to treat AIDS and conditions associated with HIV infection. Claim 71, is directed to the pharmaceutical composition of claim 67 wherein the tat protein has the sequence of SEQ ID. NO. 2.

Claim 76, upon which claims 77-81 depend, is directed to biologically active isolated tat protein. Claim 77 is directed the tat protein of claim 76 that is lyophilized for storage and re-suspended in a biologically acceptable fluid for use. Claim 78 is directed to the tat protein of claim 76 that is lyophilized and re-suspended in a biologically acceptable fluid for use as a vaccine. Claim 79 is directed to the tat protein of claim 76 wherein the tat protein has the sequence of SEQ. ID. NO. 2. Claim 80 is directed to the use the tat protein of claim 76 in treating AIDS and conditions associated with HIV infection. Claim 81 is directed to the use of mutants of the tat protein of claim 79 in treating AIDS and conditions associated with HIV infection.

Newly added claim 82, upon which newly added claims 84-88 depend, is directed to a vaccine composition comprising isolated biologically active tat protein that is non-aggregated and non-oxidized in an amount that is effective to induce an immune response. Claim 83 is directed to the tat protein of claim 82 wherein the tat protein has the sequence of SEQ. ID. NO. 2. Claim 84 is directed to the vaccine composition of claim 82 or 83 wherein the composition is lyophilized. Claim 85 is directed to the lyophilized vaccine composition of claim 84 which is resuspended in a pharmaceutically acceptable fluid for use. Claim 86 is directed to the vaccine composition of claim 82 or 83 wherein the composition is suitable for different routes of administration. Claim 87 is directed to the vaccine composition of claim 82 or 83 wherein the biologically active tat protein is purified using a process that prevents oxidation and aggregation of tat protein. Claim 88 is directed to the vaccine composition of 87 wherein the biologically active tat protein is purified using heparin affinity chromatography.

B. <u>Claims 62-72 and 76-81 Are Operable and Useful Under 35 U.S.C. § 101</u>

Claims 62-72 and 76-81 are rejected as allegedly disclosing an inoperative invention under 35 U.S.C. § 101. Office Action, p. 4. The Examiner alleges that the invention disclosed is inoperative because the inherent difficulties of developing an HIV vaccine or preventing HIV infection are well known and the specification fails to teach or describe the use of the invention as a vaccine. First Office Action, pp. 3-4.

35 U.S.C. § 101 requires that an invention must be useful. Evidence of utility is sufficient if it leads one of ordinary skill in the art to conclude that the asserted utility is more likely true than not. MPEP § 2107.02. For pharmacological or therapeutic utility, an applicant is only required to provide evidence that reasonably supports the asserted utility, that is, the applicant is required to produce evidence that shows a reasonable correlation between the pharmacological or other biological activity and the asserted therapeutic use. MPEP § 2107.03, citing to *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Jolles*, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *Nelson v. Bowler*, 206 U.S.P.Q. 881 (C.C.P.A. 1980). An applicant is not required to provide utility beyond a reasonable doubt or establish that the asserted utility is statistically certain. See *In re Irons*, 144 U.S.P.Q. at 354 and *Nelson,* 206 U.S.P.Q. at 883-885. Proof of some desirable pharmaceutical property of a compound in a standard experimental model is sufficient evidence of a therapeutic utility even though it may eventually be found that the compound is not useful in treatment of humans. *In re Brana*, 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). For a specific use of an invention for treatment in humans, utility is shown by demonstration of the desired pharmaceutical effect in *in vivo* animal models accepted by those in the art to be predictive of effectiveness in humans. *Jolles*, 206 U.S.P.Q. at 890.

Thus, in accordance with the case law discussed above, a showing of the desirable pharmaceutical activity of the present invention in a standard experimental model is sufficient to meet the utility requirement of 35 U.S.C. § 101 for claims 62-72 and 76-81.

1. Present Invention Addresses "Inherent Difficulties" of Past HIV Vaccine Research

The Examiner rejects claims 62-72 and 76-81 as allegedly disclosing an inoperative invention under 35 U.S.C. § 101. Final Office Action, p. 4. As one ground for the rejection, the Examiner cites his reason in the Office Action dated January 16, 2002 ("First Office Action"). In the First Office Action, the Examiner states that the specification only contains "prophetic statements regarding the use of the invention for preventing or treating as well as a vaccine for HIV related diseases, [but the specification]...fails to teach, nor does it describe such use." First Office Action, p. 3.

A rejection under § 101 requires that the asserted utility be contrary to scientific principle or wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (citing *In re Chilowsky*, 108 U.S.P.Q. 321 (C.C.P.A. 1956). The Examiner states that "difficulties inherent to development of an HIV

vaccine or preventing infection are well known" and, thus, one or ordinary skill in the art would require clinical, *in vivo*, or *in vitro* data before accepting the truth of the asserted utility of the invention as a vaccine for HIV. First Office Action, pp. 3-4. In particular, the Examiner notes the following five problems associated with the development of an HIV vaccine: (1) extensive genomic diversity associated with the HIV retrovirus; (2) virus is transmitted from cell to cell in covert form; (3) the virus exists in latent forms; (4) the disease is complex; and (5) portions of HIV proteins cause immunosuppression or other detrimental consequences . First Office Action, p. 4. Applicants respectfully submit that the present specification discloses a valid utility of the invention as an HIV vaccine and provides sufficient support, including *in vivo* and *in vitro* data, to convince one of ordinary skill in the art of the truth of the asserted utility. *Jolles*, 206 U.S.P.Q. at 890 (citing *In re Irons*, 44 U.S.P.Q. 351 (C.C.P.A. 1965)).

The problems with HIV vaccine research that were cited by the Examiner apply to vaccine studies targeting HIV envelope proteins, which have failed to protect against heterologous viruses because of the variability of the envelope proteins among different virus strains. Cafaro *et al.*, 2000, *J. Med Primal* 29:193-208 ("Ref. BB").[1] In contrast, vaccines based on structural HIV proteins that have key roles in the virus life cycle overcome these "inherent difficulties." In particular, the attractive features of tat protein for vaccine therapy are: (1) tat protein is expressed early in the virus life cycle and is necessary for viral replication and transmission; (2) there is correlation between anti-Tat immune response and the nonprogression of AIDS in HIV-infected individuals; (3) tat protein is readily taken up by professional antigen presenting cells ("APCs") and is presented in the context of major histocompatibility complex ("MHC") class I; (4) tat protein is conserved among geographically distinct HIV isolates; and (5) tat protein vaccination has been shown to be safe in standard animal models. See Specification, p., 2, ll. 7-13 and Fanales-Belasio, *et al.*, 1996, *DNA and Cell Biology*, 21: 599-610. Feature (1) addresses the problems (2) and (3) cited by the Examiner because vaccination against tat protein, which is critical for viral replication, would reasonably inhibit viral transmission between cells and prevent latent viruses from becoming active. Features (1) and (4) address problems (1) and (4) cited by the Examiner because tat protein is a highly conserved protein expressed early in the viral life cycle and is necessary for viral replication and transmission. Feature (5) addresses problem

[1] Referenced cited herein are submitted with the enclosed Supplemental Information Disclosure Statement and are referred to by their reference identifiers.

(5) cited by the Examiner because administration of biologically active tat protein has been shown to be safe in standard animal models. Thus, the problems that the Examiner cites as being "inherent" in HIV vaccine development are reasonably overcome by HIV vaccines based on the tat protein. Therefore, Applicants' asserted utility of the invention asserted in claims 62-72 and 76-81, as required for a rejection under §101, does not violate a scientific principle nor is it wholly inconsistent with contemporary knowledge in the art. *Gazave*, 154 U.S.P.Q. at 96.

For the reasons stated above, Applicants respectfully request that the rejection of claims 62-72 and 76-81 under 35 U.S.C. § 101 be withdrawn.

2. Monkey Models are Predictive of Human Therapy

The Examiner states that in order to provide proof of utility with regard to drugs and their uses, an applicant must provide data from either clinical, *in vivo*, *in vitro*, or a combination sufficient to convince one of ordinary skill in the art of that the asserted utility is sufficiently established. First Office Action, p. 4. In response to the First Office Action, Applicants argued that examples using monkey SHIV models presented in the specification showed that the present invention was operable and useful. Final Office Action, pp. 4-5. However, the Examiner rejects this argument, stating that although Applicants have shown that monkeys challenged with SHIV can be used to study various aspects of HIV, Applicants have failed to show how effectiveness as a vaccine in monkey SHIV models corresponds to effectiveness as a vaccine in humans infected with HIV. Final Office Action, pp. 5-6.

Applicants respectfully assert that it is well known and accepted in the art that monkey SHIV models are models for human HIV treatment. Human clinical trials are not required to prove utility in treatment of humans if such utility is supported with *in vivo* animal models that are accepted by those in the art as screening procedures for testing new drugs for humans. *Jolles*, 206 U.S.P.Q. at 890. An applicant is only required to provide evidence that the pharmacological or other biological activity of a compound reasonably correlates to the asserted therapeutic utility and is not required to prove the utility beyond a reasonable doubt or statistical certainty. MPEP § 2107.03; *Nelson v. Bowler*, 206 U.S.P.Q. 881 (C.C.P.A. 1980); *In re Irons*, 144 U.S.P.Q. 351 (C.C.P.A. 1965). In *In re Brana*, the Federal Circuit Court of Appeals stated that "it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it

may eventually appear the compound is without value in the treatment of humans." 34 U.S.P.Q.2d at 1442 (quoting *In re Krimmel*, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961)).

Monkey models are considered essential tools in the development of vaccines by persons of ordinary skill in the art. *See* Stott *et al.*, 1998, *AIDS Research and Human Retroviruses*, 14(3):S-265-S-270 ("Ref. BL"). Many observations originally made in monkey models have been confirmed in clinical studies of HIV-infected patients. Ref. BL at S-265, col. 1. Since, as the Examiner notes on p. 5 of the Final Office Action, HIV-1 is incapable of infecting monkeys, the Simian Human Immunodeficiency Virus ("SHIV") was developed to enable testing of HIV vaccine candidates in the monkey model. Lu, 1997, *Critical Reviews in Oncogenesis*, 8(2&3):273-291, at 280, col. 1 ("Ref. BH"). SHIV is a recombinant virus comprising SIV in which the SIV *env, tat,* and *rev* genes are replaced with their HIV-1 counterparts. *Id.* at p. 280, col. 2. Infection of monkeys by the simian immunodeficiency virus ("SIV") is similar in virology, immunology, and pathogenesis of the human immunodeficiency virus ("HIV-1") in humans. Ref. BL at S-265, col. 1. SHIV 89.6, used in the examples of the present specification, is particularly useful for studying HIV-1 vaccine efficacy because, like HIV-1, it is capable of infecting monkeys by intravaginal inoculation. Ref. BH at p. 280, at col. 2.

Although, those in the art acknowledge that HIV vaccines that are effective in animal models may be ineffective when tested in humans, the value of such animal models in development of human HIV therapies is not questioned. For example, Nath *et al.* (2000, *Trends Microbiol.*, 8(9):426-31) ("Ref. BJ") states that even if a vaccine shows 100% efficacy in non-human primate models, it may still be ineffective in humans. But Ref. BJ also states that "non-human primates are excellent models for human disease because they exhibit remarkable similarities to humans in virtually every aspect of their anatomy, physiology, and endocrinology." Johnston (2000, *Molecular Medicine Today*, 6:267-270) ("Ref. BG") also discusses improvements that could be made in the macaque model, but notes that "evaluation of vaccines in HIV/AIDS animal models is an essential component of a comprehensive vaccine research and development program." Doubt of the predictive value of animal models for human therapy is permitted, as long as the animal models contribute to the increasing human cure rate. See *Brana*, 34 U.S.P.Q.2d at 1442. Thus, positive results in an animal model accepted as useful in the art are sufficient to demonstrate utility.

For the reasons stated above, Applicants respectfully submit that monkey SHIV models, used in working examples in the specification, are accepted by those in the art as valid models for HIV vaccine development. Thus, the showing of the effectiveness of the

present invention as a vaccine in the SHIV monkey model is sufficient to show utility for claims 62-72 and 76-81. As discussed below in Section B.3, *infra*, claims 62-72 and 76-81 are operable under 35 U.S.C. § 101.

3. Specification Provides Sufficient Evidence of Effectiveness of Invention as a Vaccine Against HIV

The Examiner rejects the *in vivo* tests in the specification stating that the tests did not prove that the invention acted against HIV because the monkeys were vaccinated against HIV tat, and not HIV. Final Office Action, p. 5. The Examiner further states that the *in vivo* tests showed only that the immunized monkeys were not harmed and exhibited an immune response that was not necessarily a protective response. Final Office Action, p. 5. Applicants respectfully disagree.

Applicants respectfully note that a showing of the desired pharmacological activity in a standard animal model is sufficient to meet the utility requirement of 35 U.S.C. § 101. See *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) and *In re Jolles*, 206 U.S.P.Q. 885 (C.C.P.A. 1980). As discussed above, the monkey SHIV model is a standard animal model for development of human HIV therapy. The specification presents examples in which administration of the biologically active tat protein of the present invention to monkeys infected with SHIV elicit protective immune responses against HIV infection. Thus, the present invention recited in claims 62-72 and 76-81 is operable and useful as required by 35 U.S.C. § 101.

Applicants respectfully draw the Examiner's attention to Example 4 of the specification. In Example 4, three monkeys were immunized with 10 μg of biologically active tat protein in 250 μl of autologous serum and 250 μg of RIBI, three monkeys were immunized with 10 μg of biologically active tat protein in 250 μl of autologous serum and 250 μl of alum, and two monkeys served as controls. All monkeys were then infected with the chimeric virus SHIV 89.6P containing the HIV-1 tat gene and monitored for virological parameters. Specification, pp. 51-52.

The Examiner states that the *in vivo* tests do not prove that the invention acted against HIV because the monkeys were vaccinated against HIV tat and not HIV. Final Office Action, p. 5. However, as discussed above in Section III.A, *supra*, tat protein is essential for HIV transmission and replication. Thus, strong immune responses against tat protein would likely inhibit HIV transmission and replication.

Example 4 shows that the present invention induced protective immune responses in the standard SHIV monkey model which is accepted by those in the art as standard models for development of human HIV vaccine therapies. Four out of the six monkeys immunized with biologically active tat protein of the present invention did not become infected by SHIV 89.6P, whereas both control monkeys became infected. Specification, p. 65. The monkeys immunized with biologically active tat protein of the present invention also produced high levels of anti-Tat antibody (*e.g.*, IgG). Specification, p. 52, ll. 29-31. Anti-Tat antibodies have been shown to be protective against AIDS in HIV-infected humans vaccinated with tat DNA in Calarota *et al.*, 1999, *J. Immunology*, 163(4):2330-2338 ("Ref. BC"). The monkeys vaccinated in Example 4 also displayed stronger cytotoxic T cell responses ("CTL") compared to control monkeys, particularly overall increase in CD8+ lymphocyte ("CAF") antiviral activity. Specification, pp. 58-60. CTLs have been shown to contain HIV-1 replication early in the infection and the decrease of CTLs is associated with the onset of symptoms of HIV. See Calarota, 1998, The Lancet, 351:1320-1325 ("Ref. BD"); Ref. BC. CD8+ T cells have been shown to protect against productive HIV-1 infection. See Wang *et al.*, 2002, Virology, 304(2):246-64 ("Ref. BM") and McMichael and Rowland, 2001, Nature, 410:980-987 ("Ref. BI"). Therefore, Example 4 provides sufficient evidence to convince one of skilled in the art that the present invention produces a protective pharmacological activity in the monkey SHIV model to support the conclusion that the present invention is operable and useful.

The United States Court of Customs and Patent Appeals stated that an "adequate proof of any such [pharmacological] activity constitutes a showing of practical utility." *Nelson*, 206 U.S.P.Q. at 883. Example 4 of the specification show that the administration of the present invention, biologically active tat protein, to monkeys in a standard SHIV monkey model induces increase in levels of CTLs, a pharmacological activity. The Federal Circuit Court of Appeals stated in *In re Brana* that a showing of some desirable pharmaceutical property in a standard experimental animal is sufficient to show utility. 34 U.S.P.Q.2d at 1442. Example 4 of the specification show that administration of the biologically active tat compositions of the present invention induces in the standard SHIV monkey model increased levels of CTLs that have been shown to be protective against HIV infection. Thus, Applicants respectfully submit that utility for claims 62-72 and 76-81 is shown by the present specification and request that the rejection under 35 U.S.C. § 101 be withdrawn.

C. **Claims 62-72 and 76-81 Are Enabled Under 35 U.S.C. § 112, First Paragraph**

Claims 62-72 and 76-81 are rejected under 35 U.S.C. § 112, first paragraph as non-enabling for vaccines for treating or preventing HIV related diseases. Final Office Action, p. 6. Rejections under 35 U.S.C. § 101 for lack or utility are related to rejection under 35 U.S.C. § 112 for lack of enablement since if an invention is considered to be inoperative under § 101, a person skilled in the art cannot practice the invention and therefore, § 112 enablement requirement is not met. *In re Swartz*, 56 U.S.P.Q.2d 1703, 1704 (Fed. Cir. 2000). For the reasons stated above in Section B, Applicants respectfully submit that the present invention is operable under 35 U.S.C. § 101 and that the specification provides sufficient guidance for one in skilled in the art to practice the present invention with reasonable expectation of success.

The Examiner states similar reasons for his rejection of claims 62-72 and 76-81 under §112 for non-enablement as he did for his rejections under § 101 for lack of utility. Final Office Action, pp. 6-11. The Examiner rejects Applicants' evidence of the effectiveness of the invention in treating SHIV infection in monkeys, alleging that success in the SHIV monkey model does not provide reasonable expectation of success in human treatments. Final Office Action, p. 10. The Examiner further alleges that the examples of the specification only show that an immune response was induced, but does not show that the immune response is protective against HIV. Final Office Action, p. 9. The Examiner did not cite any references in the First Office Action or the Final Office Action which teach that the SHIV monkey model is not a standard model for studying HIV and developing HIV vaccines.

The specification teaching how to make and use the claimed invention must be taken as enabling under § 112 unless the Examiner show that there is reason to doubt the objective truth of statements contained therein. *Brana*, 34 U.S.P.Q.2d at 1441 (quoting *In re Marzochhi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971)). The enablement requirement of 35 U.S.C. § 112 is met when in view of the specification and what is known in the art, practicing the invention does not require undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the art. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine or the specification provides reasonable amount of guidance and direction to the experimentation. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Pat. Bd. App. 1982); *Hybritech*

Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The unpredictability of the result of an experiment, however, is not a consideration. *In re Angstadt*, 190 U.S.P.Q. 214, 217-218 (C.C.P.A. 1976). In the present case, as set forth below, the disclosure provides sufficient direction and guidance and, thus, the claims are enabled.

Applicants respectfully submit that claims 62-72 and 76-81 are fully enabled and respectfully request that the rejection of these claims for non-enablement be withdrawn. Applicants incorporate her discussion of these claims in Section B that show that the present invention is operable and useful in the treatment of HIV associated diseases to support their request in addition to the arguments made below.

1. Monkey Models are Valid Models for Human Therapy

The Examiner rejects Applicants' *in vivo* studies using SHIV monkey model as valid support for enablement of claims 62-72 and 76-81. The Examiner alleges that Applicants make an unsubstantiated assertion that monkeys are essentially model substitutes for human treatments. Final Office Action, p. 10. The Examiner also alleges that success in the monkey model does not produce a "reasonable expectation of success" in humans. *Id.* In particular, the Examiner points out that in the monkey model, monkeys are infected with SHIV, not HIV and therefore do not enable the present invention as a vaccine for HIV. Final Office Action, p. 9. In effect, the Examiner is stating that unless an animal is infected with HIV, an invention for treatment of HIV is not enabled. However, an animal model infected with HIV, such as the HIV-mouse model, is not the only model accepted by one of skilled in the art as a valid model for developing human HIV treatments. Any experimental animal model acceptable by those skilled in the art can be used to show enablement. *Brana*, 34 U.S.P.Q.2d at 1442. As discussed in Section B.2, the SHIV monkey model is considered by those skilled in the art as a standard experimental model for human HIV.

The Examiner states that "the only challenge studies were with an artificial virus construct in animals that do not get infected with HIV and progress to AIDS." Final Office Action, p. 9. Since monkeys are not naturally susceptible to HIV infection, as pointed out by the Examiner, SHIV was developed to enable the study of HIV vaccines in the monkey model. Ref. BH at p. 280, col. 1. As discussed in Section III.B.2, *supra,* SHIV is a chimeric virus comprising SIV in which the SIV *env, tat,* and rev genes are replaced with their HIV-1 counterparts, thus SHIV is an HIV virus that is capable of infecting monkeys and causing simian AIDS. *Id.* at p. 280, col. 2. Many observations originally made in monkey

models have been confirmed in clinical studies of HIV-infected patients. Ref. BL at S-265, col. 1.

Example 4 of the specification shows that the present invention induced protective immune responses in the standard SHIV monkey model. Four out of six monkeys immunized with biologically active tat protein of the present invention did not become infected when challenged with SHIV 89.6P and displayed higher levels of anti-tat antibodies and CTL responses which have been shown in the to be protective against HIV. See discussion in Section B.3, *supra*. Since the SHIV monkey model is a standard model used for HIV vaccine development, one of ordinary skilled in the art would reasonably expect the same positive results in humans.

In addition, tat cDNA immunization, which, like the present invention, induces protective immune responses against HIV-1 tat, has been shown to induce protective immune responses in humans infected with HIV. Ref. BC and Ref. BD. HIV-1 infection results in the early loss of specific Th cell responses to HIV-1 antigens followed by reduction of T cell responses to most antigens in humans. Ref. BC at p. 2330, col. 1. DNA-based immunization was shown to be effective in animal models to induce humoral and cellular responses that provide protection from infectious challenge. *Id.* Administration of tat cDNA vaccines to humans infected with HIV showed similar results. In the study presented in Ref. BD, HIV infected patients immunized with tat cDNA displayed increased HIV-1 specific cellular responses and increased levels of antigen-specific precursor CTLs. Ref. BD at p. 1324, col. 1. In the study discussed in Ref. BC, vaccination of HIV-1 infected patients with tat cDNA induced increased levels of HIV-specific antibodies, T cell proliferation, and CTL responses, which were absent before immunization. Ref. BC at p. 2336, col.2.

As discussed above, Example 4 in the specification shows that the administration of the present invention, biologically active tat protein, as defined the specification, induces increased levels of CTLs, which have been shown in the art to be protective against HIV. See Ref. BI and Ref. BM. In contrast to the results obtained by Applicants, two studies indicate that vaccination against tat protein do not induce protective immune responses following viral challenge. However, these conflicting results are easily explained.

In Silvera *et al.*, 2002, *J. Virology*, 2002: 3800-3809 ("Ref. BK"), rhesus monkeys that were immunized with tat protein failed to induce protective immune responses in the monkeys when challenged with SHIV 89.6P. *Id.* at p. 3807, col. 2. There is no discussion in Ref. BK as to how the tat protein used for vaccination was isolated, and as

discussed previously, the tat protein of the invention is defined by the specification as "biologically active tat protein." If the tat protein used in Ref. BK were oxidated or aggregated, then it not the biologically active tat protein of Applicants' invention. The researchers in Ref. BK also point out that their study differed in several ways from that of Applicants' published studies involving tat protein vaccination. *Id.* at p. 3808, col. 1. In particular, researchers in Ref. BK stated that they used less-extensive immunization regimens that Applicants, did not administer adjuvants, and used rhesus and not cynomologus monkeys. *Id.* The researchers in Ref. BK further noted that their study "may underestimate the potential for tat to confer protection." *Id.*

In Allen, 2002, *J. Virology*, 76(8):4108-4122 ("Ref. BA"), vaccination of rhesus macaques with tat DNA induced higher level of Tat-specific CTL, but did not control of SIV infection. Ref. BA, p. 4108. As discussed above, vaccination with tat cDNA has been shown in humans to induce protective immune responses. The study presented in Ref. BA cannot be compared to the data provided in the present specification or studies discussed in Ref. BC and Ref. BD. In study in Ref. BA, the rhesus monkeys were vaccinated with DNA encoding SIV tat and not HIV-1 tat. Ref. BA, p. 4108. The researchers in Ref. BA, themselves, caution readers in interpreting the results of this experiment since the rhesus monkeys were infected challenged with highly pathogenic molecular clone and the study was not designed to induce CD4 T-cell helper responses that play an important role in containment of HIV and SIV infections. *Id.* at p. 4111.

For these reasons, Ref. BK and Ref. BA do not detract from the teachings of the specification that "biologically active tat protein" of the present invention is effective in treating HIV related diseases.

Based on the discussion above, Applicants respectfully assert that the SHIV monkey model is a standard model for human HIV therapy. The present specification discloses examples showing the effectiveness of the present invention in inducing protective immune responses against HIV in the SHIV monkey model as discussed in Section B.3, *supra*. Therefore, the present invention is fully enabled by the specification since one of ordinary skill is fully enabled to make and use the present invention with reasonable expectation of success.

2. <u>Claims To Vaccine for HIV Are Fully Enabled</u>

The Examiner alleges that the present invention is not enabled because although Applicants have shown that immunization with biologically active tat protein

produces an immune response, they have not shown that it produces a protective response. Final Office Action, p. 8. The Examiner then provides three definitions of a "vaccine." *Id.* Applicants respectfully submit that the specification fully enables claims 62-72 and 76-81.

The Examiner states that "although nearly any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined." Final Office Action, p. 8. The Examiner defines prophylaxis as "the prevention of disease or of a process that can lead to a disease." Applicants respectfully point out that the prophylactic quality of the present invention has been experimentally shown. In Example 4 of the specification, as discussed above, four out of six monkeys administered vaccine compositions of the present invention did not become infected when challenged with SHIV 89.6P expressing HIV-1 Tat. In addition, vaccinated monkeys had higher levels of anti-Tat antibodies and other protective antibodies in comparison to non-vaccinated monkeys. Specification, Example 4. This demonstrates that the present invention prevents the development of AIDS and therefore is prophylactic.

The Examiner also states that the *Illustrated Dictionary of Immunology* defines "vaccine as a composition that stimulates protective antibodies and T cell immunity and induces active immunity." Applicants respectfully draw Examiner's attention to Example 4 of the specification once more. Monkeys vaccinated with the present invention displayed higher levels of specific anti-HIV antibodies (*e.g.*, IgM, IgG) and greater CTL responses than control monkeys when challenged with SHIV. Specification, p. 52-60. As discussed above, high levels of CTL responses have been shown to be protective against HIV infection and related diseases. See Ref. BI and Ref. BM. Since the present invention stimulates the protective antibodies and T cell immunity, according to the definition cited by the Examiner, the present invention is a vaccine.

For the reasons stated above, Applicants respectfully submit that the present invention is enabled and respectfully request that rejection of claims 62-72 and 76-81 under 35 U.S.C. § 112 be withdrawn.

3. Specification Provides Sufficient Guidance to One of Ordinary Skill in the Art to Overcome Unpredictability

Examiner states that the ability of a vaccine to raise a protective immune response depends on the structure of the protein and since a single amino acid can alter the structure of the protein, the structure and function of a protein cannot be predicted. Final

Office Action, p. 10. For this reason, Examiner rejects claims 62-72 and 76-81 as non-enabling. Final Office Action, p. 6.

The Examiner cites to *Fundamental Immunology* as teaching that the measurement of the mobility of native protein is dependent on availability of high resolution crystal structure, so applicability is limited to only a small subset of proteins. Final Office Action, p. 9. Examiner cites to Riffkin *et al.* as teaching that a single amino acid change can alter the structure of a protein dramatically. Final Office Action, p. 10. The Examiner also cites to Abaza *et al.* as teaching that mutations outside the antigenic epitope exert an effect on the structure of the epitope and thus change the functionality of the protein. *Id.* Therefore, Examiner alleges that the present invention is not enabled because a small mutation in the protein can change the protein structure, making the structure unpredictable, and since protein structure determines protein functionality, protein functionality cannot be predicted either. Final Office Action, pp. 10.

Applicants respectfully point out that an invention is enabled under 35 U.S.C. § 112 if it provides sufficient guidance for one in the art to practice the invention without undue experimentation. Although unpredictability of the art can be considered in determining the level of "undue experimentation,." the mere unpredictability of an experiment is not a consideration. *In re Angstadt,* 190 U.S.P.Q. 214 (C.C.P.A. 1976). The specification defines "biologically active tat protein" of the claimed invention by its function and provides one of skill in the art with sufficient guidance to test isolated tat protein for each of the functional points and determine whether the isolated tat protein is "biologically active" as defined in the specification. Specifically, Example 1 of the specification provides one of ordinary skill in the art a non-limiting example of how to isolate biologically active tat protein of the invention and how to test whether an isolated tat protein is indeed biologically active as defined by the specification. See Specification, pp. 24-34. Thus, whether or not the structure of tat protein can be predicted is irrelevant in determining whether the present claims are enabled under 35 U.S.C. § 112. The specification provides sufficient direction and guidance to one of ordinary skill in the art to practice the present invention without undue experimentation and with reasonable expectation of success. *In re Wands*, 8 U.S.P.Q.2d at 1404.

For the reasons stated above, Applicants respectfully submit that claims 62-72 and 76-81 are enabled by the present specification and patentable under 35 U.S.C. § 112. Accordingly, Applicants respectfully request that the rejection of these claims be withdrawn.

D. **Claims 62, 65-68, 72, 76, and 79 Are Patentable over U.S. Patent N . 5,652,122 by Frankel *et al.* Under 35 U.S.C. § 102(a)**

The Examiner rejects claims 62, 65-68, 72, 76, and 79 as allegedly anticipated by U.S. Patent No. 5,652,122 to Frankel *et al.* ("Frankel"). Final Office Action, p. 11. Applicants respectfully disagree.

35 U.S.C. § 102(a) states that a person is entitled to a patent unless the invention was known or used by others in this country, patented, or described in a printed publication before the invention thereof by the applicant. The Federal Circuit Court of Appeals states that a rejection under § 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." *In re Paulsen*, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994).

The Examiner alleges that Frankel teaches a wild type variant tat protein and the various limitations in claims 62, 65-68, 72, 76, and 79 on the tat protein are inherent characteristics of the wild-type tat protein. First Office Action, p. 11. The Examiner explains further that since the Applicants' claims do not distinguish the structure of biologically active tat protein of the invention from wild type tat protein, Frankel anticipates. First Office Action, pp. 11-12.

Frankel discloses the use of HIV tat proteins or tat-derived polypeptides to deliver molecules ("cargo molecules") of interest (*e.g.*, therapeutic molecules) into eukaryotic cells. Frankel, col. 2, ll. 65-67. Frankel does not teach the use of tat protein with the activity of the wild type variant tat protein. In particular, Frankel teaches that the second exon of the tat protein is not required for activity and teaches the use of tat fragments without the second exon in the therapeutic methods Frankel describes, *i.e.*, delivery of cargo molecules. Frankel, col. 20, ll. 19-23. Frankel further teaches that problems of oxidation and aggregation are solved by deleting cysteine residues and that removal of the tat cysteine-rich regions have "the additional advantage of eliminating the natural activity of tat." Frankel, col. 9, l. 47 to col. 10, l. 38; Frankel, col. 9, l. 65 to col. 10, l. 1. In describing purification of wild type tat (see Example I), Frankel does not specifically teach or caution against oxidation and aggregation of the tat protein. See Frankel col. 20, ll. 13-43.

Applicants respectfully note that a rejection under 35 U.S.C. § 102 requires that "each and every limitation of the claimed invention be disclosed in a single prior art reference." *In re Paulsen,* 31 U.S.P.Q. 2d 1671, 1673 (Fed. Cir. 1994). In contrast to Frankel, Applicants teach in their specification and claim in claims 62, 65-68, 72, 76, and 79 a biologically active tat protein. Claims 62, 65-68, 72, 76, and 79 claim a biologically active

tat protein that (1) enters activated endothelial cells or dendritic cells at concentrations up to 10 nM and (2) performs at least one of the following actions (i) activates the proliferation, migration, and invasion of Kaposi's sarcoma (KS) cells or cytokine-activated endothelial cells, (ii) activates virus replication when added to infected cells as measured by (a) the rescue of Tat-defective proviruses in HLM-1 cells after the addition of exogenous protein and/or (b) the transactivation of HIV-1 gene expression in cells transfected with HIV-1 promoter-reporter plasmid, and (iii) induces in mice the development of KS-like lesions in the presence of angiogenic factors or inflammatory cytokines.

Frankel does not disclose that the tat protein of its invention has the same capabilities as the biologically active tat protein of Applicants' invention. Frankel teaches one of ordinary skill that tat protein without the natural activity of wild type tat should be used in the methods of its invention, *i.e.*, delivery of cargo molecules. Frankel teaches that the second exon of the tat protein is not required for tat activity, whereas the Applicants teach that the second exon, particularly the RGD motif, is required for the tat protein to be biologically active as defined by the Applicants. Frankel, col. 20, ll. 19-23; Specification p. 33, l. 26 to p. 34, l. 2. In addition, Frankel does not explicitly teach that precautions must be taken to prevent oxidation and aggregation of tat protein, whereas the Applicants teach that purification of tat protein using a process that prevents oxidation and aggregation of the tat protein, since tat protein must be non-oxidized and non-aggregated in order to be biologically active. Frankel, col. 20, ll. 13-43; Specification, pp. 24-25. Since Frankel does not disclose each and every limitation, Frankel does not anticipate claims 62, 65-68, 72, 76, and 79. See *In re Paulsen*, 31 U.S.P.Q.2d at 1673.

However, the Examiner also alleges that Frankel inherently anticipates claims 62, 65-68, 72, 76, and 79. The Examiner states that although Frankel does not specifically state that the tat protein disclosed by Frankel enters a particular cell at a particular concentration, "it does not mean that it does not happen, it was not tested. These are characteristics of the protein." Final Office Action, p. 14.

A reference inherently anticipates if the missing descriptive matter is (1) necessarily present in the thing described in the reference and (2) it would so be recognized by persons of ordinary skill. See MPEP § 2112 and *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950-1951 (Fed. Cir. 1999) (citing *Continental Can Co. v. Monsanto Co.*, 20 U.S.P.Q.2d 1746, 1749 (Fed Cir. 1991)).

The Examiner states that the characteristics used to define Applicants' biologically active tat protein is inherent in the protein. However, the tat protein disclosed by

Frankel for use in transporting "cargo molecules" and the tat protein of Applicants invention are different, and the functionalities of the two proteins are different. Frankel teaches that the second exon of the tat protein is not required for activity and teaches fragments lacking in the second exon for delivery of cargo molecules, *i.e.*, for therapeutic use. See Frankel, col. 20, ll. 19-23. In Examples 1-17 presented in Frankel, only tat protein fragments comprising the first exon (amino acids 1-72), and not the second exon, are used as carriers of cargo molecules. Frankel, col. 25-54. However, tat protein without the RGD sequence, which is coded in the second exon (amino acids 73-86), is not "biologically active" as recited in the claims and defined by Applicants' specification. Specification, p. 33, l. 26 to p. 34, l. 2. The RGD motif of biologically active tat protein mediates uptake of tat protein by endothelial cells and dendritic cells at low concentrations through interactions of the RGD sequence with $\alpha_5\beta_1$ and $\alpha_v\beta_3$ receptors. *Id.* Without the RGD motif, cells can only uptake tat protein at high concentrations through integrin-independent pathways. *Id.* The Examiner states that presence of the RGD motifs is not a claim limitation. Final Office Action, p. 14. However, the recitation of "biologically active tat protein" requires the presence of the RGD motif as discussed.

As stated above, a reference inherently anticipates if the missing descriptive matter is necessarily present in the thing described in the reference. See MPEP § 2112 and *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999). Frankel teaches that a tat protein without the second exon (*i.e.*, the RGD motif) is active and teaches such tat fragments lacking the second exon for transport of cargo molecules.. Applicants disclose that biologically active tat protein requires the second exon, particularly the RGD motif, to be biologically active as defined by in the specification. Therefore, the tat fragments taught by Frankel are not "biologically active" as recited in the claims. Thus, Frankel does not inherently anticipate claims 62, 65-68, 72, 76, and 79.

For the reasons state above, Applicants respectfully request that the rejection of claims 62, 65-68, 72, 76, and 79 under 35 U.S.C. § 102(a) be withdrawn.

E. Claims 62, 63, 69, 77, and 78 are Patentable Over U.S. Patent No. 5,652,122 by Frankel *et al.* Under 35 U.S.C. § 103(a)

Claims 62, 63, 69, 77, and 78 are rejected as obvious over Frankel under 35 U.S.C. § 103(a). 35 U.S.C. § 103(a) states that an invention is rendered obvious if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains." Citing Frankel, the Examiner alleges that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to freeze dry the tat protein preparation as to safely store and ship it in a manner that is convenient to reconstitute and use." Final Office Action, p. 15. Applicants respectfully disagree.

For a rejection under 35 U.S.C. § 103, the Examiner has the initial burden of factually supporting *prima facie* conclusion of obviousness by showing that (1) the reference(s) cited suggest or motivate modification of the reference(s) to achieve the Applicants' claimed invention, (2) there must be a reasonable expectation of success, and (3) the reference(s) must teach or suggest all the claim limitations. MPEP § 2412 and § 2413. Applicants' assert that the Examiner has failed to establish a *prima facie* conclusion of obviousness because the Examiner has not shown that the cited reference, Frankel, teaches or suggests all the limitations of claims 62, 63, 69, 77, and 78.

Claim 62 is directed to pharmaceutical compositions comprising biologically active tat protein as defined by the specification. Claim 63, which is dependent on claim 62, is directed to pharmaceutical compositions comprising biologically active Tat protein, in its purified, non-oxidized, non-aggregated form, is lyophilized for storage and resuspended in fluid for use. Claim 69, which is dependent on claim 67, is directed to pharmaceutical compositions comprising biologically active tat protein isolated by a process that prevents tat protein oxidation and aggregation followed by storage of the tat protein in its purified, non-aggregated and non-oxidized form, that is lyophilized and resuspended in a degassed buffer for use. Claims 77 and 78 are dependent on claim 76 and are directed to biologically active tat protein in it purified, non-aggregated, and non-oxidized form is lyophilized for storage and re-suspended in a fluid for use as a vaccine or other use.

As the Examiner states, it is within the skill of one ordinary in the art at the time of the invention to freeze dry a preparation to safely store and ship the preparation and later reconstitute for use. Final Office Action, p. 15. However, claims 62, 63, 69, 77, and 78 are directed to the lyophilizing and reconstituting isolated biologically active tat protein, as defined by the specification, in its purified, non-aggregated, and non-oxidized form. As discussed above in Section III.D, *supra*, Frankel does not teach pharmaceutical compositions with biologically active tat protein recited in the claims. In fact, as discussed Section III.D, *supra*, Frankel teaches away from Applicants' invention by disclosing that the second exon of the tat protein is not necessary for activity whereas Applicants disclose in the specification that the second exon, particularly the RGD motif, is required for tat protein of the invention

to be "biologically active." See Frankel, col. 20, ll. 19-23; Specification p. 32, ll. 25-30. A reference does not render a claimed invention obvious if it teaches away from the claimed invention. *In re Geisler*, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 19997). Frankel also does not teach lyophilizing tat protein in its purified, non-aggregated, and non-oxidized form.

Frankel does not teach nor suggest every limitation of claims 62, 63, 69, 77, and 78. Therefore, claims 62, 63, 69, 77, and 78 are not obvious over Frankel because (1) the Frankel does not suggest or motivate one of ordinary skill in the art to perform tests to see whether the tat protein is biologically active as defined by Applicants' specification, (2) there is no reasonable expectation of success that the tat protein disclosed by Frankel is biologically active as defined by Applicants' specification, and (3) Frankel does not teach or suggest all the claim limitations. MPEP § 2412 and § 2413.

For the reasons stated above, Applicants respectfully request that the rejection of claims 62, 63, 69, 77, and 78 over Frankel under 35 U.S.C. § 103(a) be withdrawn.

IV. CONCLUSION

It is believed that no fee is due in connection with this amendment (other than for the Extension of Time and Request for Continued Examination submitted separately herewith). However, should the Patent Office determine that a fee is due, please charge the required amount to Pennie and Edmonds LLP Deposit Account NO. 16-1150.

Applicants believe that each ground for rejection of pending claims has been successfully overcome. Accordingly, Applicants respectfully request that the following rejections be withdraw: (1) rejection of claims 62-72 and 76-81 under 35 U.S.C. § 101; (2) rejection of claims 62-72 and 76-81 under 35 U.S.C. § 112, first paragraph; (3) rejection of claims 62, 65-68, 72, 76, and 79 under 35 U.S.C. § 102(a); and (4) rejection of claims 62, 63, 69, 77 and 78 under 35 U.S.C. § 103(a).

Applicants submit that the entire application is now in condition for allowance, early notice of which would be appreciated. The Examiner is invited to telephone the undersigned should any issues remain.

Respectfully submitted,

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Enclosures